

# Exhibit 21B

[Back to Contents](#)

22



## The one rule we have to break

382 million people in the world have diabetes today. Yet half of these people have not been diagnosed and, alarmingly, it's assessed that only 6% of people with diabetes live a life free from diabetes-related complications.

**D**iabetes is an insidious disease of pandemic proportions. Ban Ki-moon, the Secretary-General of the United Nations, has described diabetes as a tsunami in slow motion. According to the latest figures from the International Diabetes Federation (IDF), 382 million people in the world have diabetes today – a number predicted to grow to close to 600 million by 2035.<sup>1\*</sup> 80% of the total number affected live in low- and middle-income countries, where the pandemic is gathering pace at alarming rates due to the lifestyle changes associated with economic growth and urbanisation.

Just as worrying is the fact that only about half of these people have been appropriately diagnosed with diabetes. This is where the 'Rule of Halves'<sup>2</sup> begins. Of those who are diagnosed, only half receive treatment from a qualified healthcare professional and again just half of these people achieve their treatment targets. Unfortunately the Rule of Halves does not end there: only half of this already relatively small group actually achieve the desired outcome and live a life free from diabetes-related complications.

The Rule of Halves estimates a global average. For some countries, eg Vietnam, Kenya and China,<sup>1</sup> diagnosis rates are even lower than 50%. For some, treatment may

be almost non-existent, while in other countries a key issue is that even those people who are diagnosed and treated do not reach their treatment targets and therefore have a high risk of developing complications. Findings from a landmark study in the UK showed that reducing blood sugar levels by close to 1% may reduce diabetes-related deaths by more than 20% and reduce microvascular complications by nearly 40%.<sup>3</sup> Microvascular complications include diabetic retinopathy, which causes more than 12,000 cases of blindness annually in the US alone.<sup>4</sup>

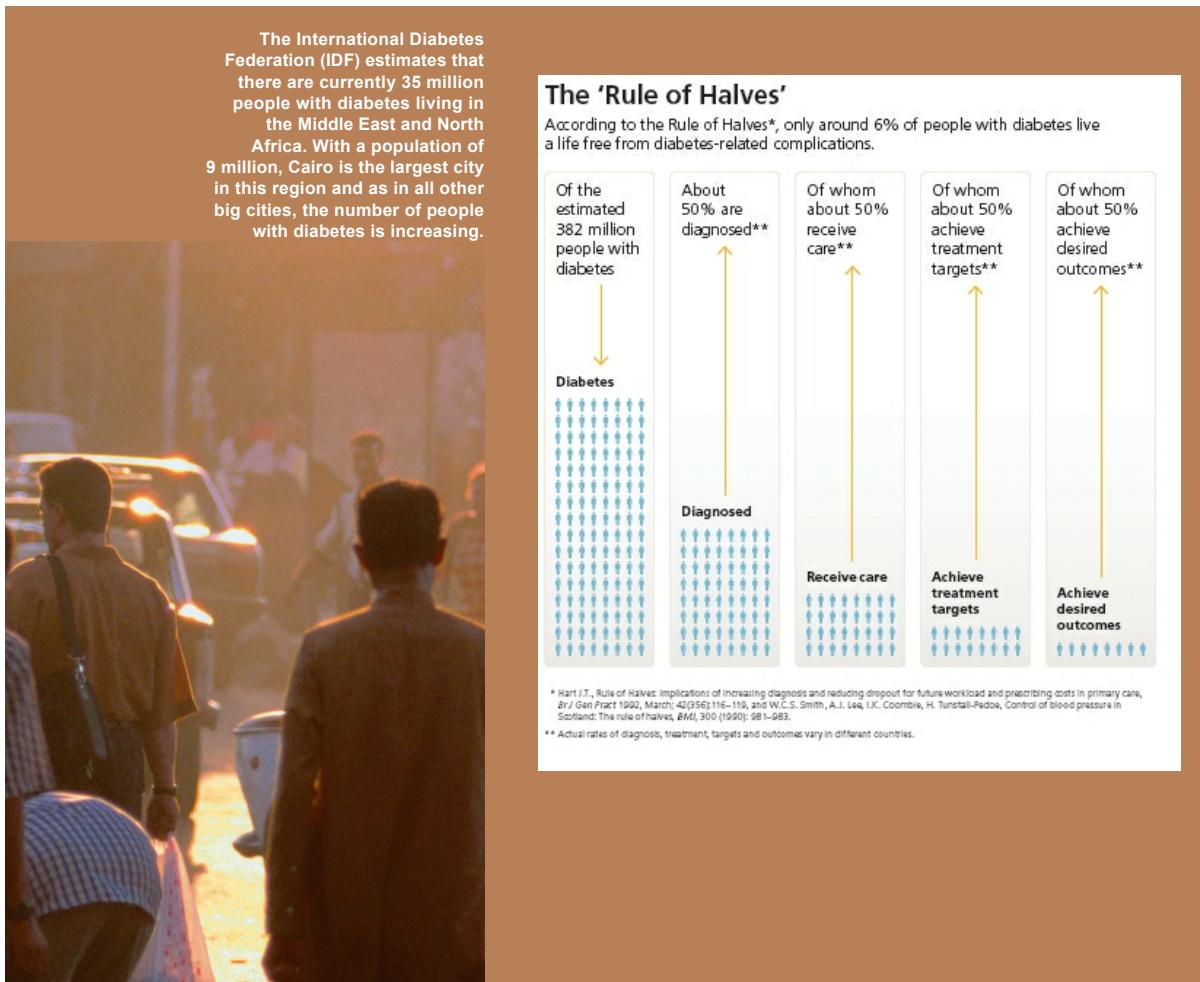
### Cannot be ignored

In human as well as financial terms, the burden of diabetes is high, being a factor in 5.1 million deaths and accounting for some 548 billion US dollars in health spending (11% of the total spend worldwide) in 2013 according to the IDF.<sup>1</sup> What all countries have in common is that the diabetes pandemic cannot be ignored. And what's important from both the human and economic perspective is that countries have a plan for how to address the Rule of Halves with a view to minimising both the personal strains and the financial burdens of diabetes. Novo Nordisk is working with governments and non-governmental organisations in many countries to help address these challenges. [Read more about Changing Diabetes® on pp 26–27.](#)

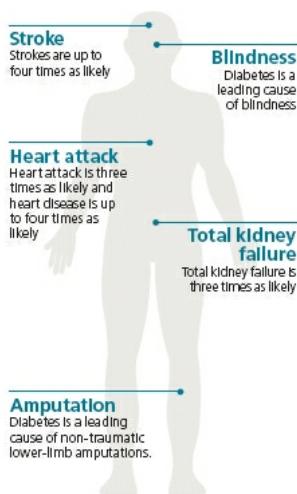
**382 MILLION PEOPLE LIVE WITH DIABETES WORLDWIDE**  
**BY 2035**  
**592 MILLION PEOPLE WILL LIVE WITH DIABETES**

\* All footnotes can be found on p 112.



[Back to Contents](#)

## Potential complications of uncontrolled diabetes



### What is diabetes?

Diabetes affects the way the body uses food for growth and energy. There are two main forms of diabetes: type 1 and type 2. Type 1 diabetes is a lifelong autoimmune disease that develops when the body produces an immune response against its own cells, destroying beta cells in the pancreas. As a result, the pancreas stops producing insulin, often – but not always – at a young age. At least 90% of people with diabetes have type 2, which is caused by a combination of lifestyle and genetic factors. People with type 2 diabetes may still produce their own insulin, but the amount is insufficient and the insulin is not used effectively by the body. Most of the long-term health complications associated with diabetes are due to persistently high blood glucose levels, which can cause damage to the kidneys, neurological system, cardiovascular system, retina or to the feet and legs through effects on both large and small blood vessels.

### How is diabetes treated?

People with type 1 diabetes need to start taking insulin as soon as they are diagnosed and must continue to do so for the rest of their lives.

People with type 2 diabetes need different treatments as the disease progresses.

Initially, lifestyle changes, including diet and exercise, and oral medicine such as metformin may be sufficient. If treatment goals are not met, GLP-1 therapy or a basal insulin (long-acting insulin) may be added. If treatment targets are still not achieved, intensive insulin treatment may be necessary. This may include adding a rapid-acting insulin at mealtimes, in addition to a basal insulin. For insulin initiation, premixed insulin with dual release to cover both mealtime and basal requirements may be used.

In total, approximately 45–50 million people worldwide are using insulin.

A significant challenge in managing diabetes with insulin is to maintain appropriate blood glucose levels, adjusting insulin dosing as necessary to balance the impact of food and exercise to avoid either high blood glucose levels (hyperglycaemia), which can lead to long-term complications such as blindness and amputations, or low blood glucose levels (hypoglycaemia), which can lead to seizures, unconsciousness or, in rare cases, death.



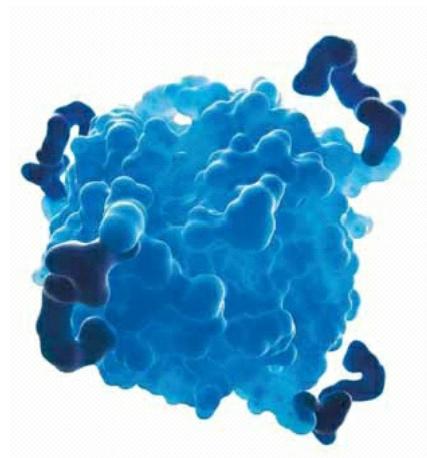
[Back to Contents](#)

With the diabetes medications available today, one may think it's easy for people with diabetes to be in optimal control of their blood sugar levels. Unfortunately it isn't that straightforward. What works for one person may not work for another. And what works for one person today may not do the job some years from now. This is why it's important to offer a wide variety of treatment options that can be tailored to each person's current needs.

Eladio Castro Garcia has started a 'peer-to-peer' diabetes information centre in his local community in Mexico. Eladio has type 2 diabetes.

[Back to Contents](#)

OTHER BUSINESS 25



**Image of the insulin degludec molecule based on X-ray crystallography data. Insulin degludec is the active compound in Tresiba®.**

**T**he fear of low blood sugar (hypoglycaemia) means that many people with type 2 diabetes are not treating their condition intensively enough to reduce blood sugar to the recommended level. Adding to this problem is the inflexibility of when injections must be taken, which can lead many people to not take insulin as prescribed. These factors can result in people with diabetes being at risk of developing severe long-term complications.

**When long is not long enough**  
A long-acting insulin is often the first step into insulin treatment for a person with type 2 diabetes – the idea is that such a ‘basal insulin’ should only need to be taken once a day, so it’s a ‘manageable’ introduction to insulin injections. One challenge, however, is that the speed at which the insulin is absorbed in the body can vary significantly from day to day in the same person. This increases the risk of hypoglycaemia, particularly at night. Another challenge is that most basal insulins do not provide an adequate level of insulin in the blood for full 24-hour coverage.<sup>1</sup>

“From speaking with many doctors and people with diabetes, we knew there was a need for a basal insulin with an ultra-long duration of action,” says Jakob Riis, executive vice president of Marketing & Medical Affairs. Tresiba® (insulin degludec)

has been designed with this need in mind. Establishing a routine for when to take insulin is important, but with a duration of action that lasts beyond 42 hours, once-daily Tresiba® provides flexibility when needed. “To be able to change the time you inject from day to day, if the situation requires, gives a remarkable sense of freedom for patients,” points out Dr Alan Moses, global chief medical officer. “And with the significantly lower risk of hypoglycaemia during the night, Tresiba® is a good example of how, even after 90 years, we can still engineer better insulin treatments.”

#### Greater than the sum of its parts

Not all people can control their diabetes with a basal insulin alone. As type 2 diabetes progresses, it may become necessary to add treatment(s) to tackle the spike in the blood sugar level that occurs

after meals too. For these people, Novo Nordisk has developed IDegLira, a combination of Tresiba® and Victoza® (liraglutide), delivered in a single daily dose. Victoza®, a human GLP-1 analogue, stimulates insulin secretion and inhibits glucagon secretion in a blood glucose-dependent manner and has also been shown to reduce body weight. In clinical trials, when IDegLira was administered once daily independently of meals, it provided improved overall glycaemic control compared with Tresiba® or Victoza® alone, with no weight change and a low rate of hypoglycaemia compared with Tresiba®. “If people aren’t getting good control on a basal insulin, IDegLira may provide the opportunity of continuing on a single daily injection of a long-acting insulin, but with the addition of Victoza®. During clinical trials, this co-formulation has been shown to work better than Tresiba® or Victoza® separately,” says Alan Moses.

Jakob Riis agrees: “IDegLira may provide a new opportunity for people with type 2 diabetes who are not adequately controlling their blood sugar levels. We believe this product will improve convenience for patients, but the development programme has also supported that the two active ingredients actually complement each other.”

In May 2013, Novo Nordisk submitted the regulatory filing for IDegLira in the EU.

#### Making Tresiba® available for patients

Tresiba® was approved in the EU in January 2013 and by the end of the year it had been launched in eight countries. In countries with broad market access, Tresiba® has quickly gained a significant share of the market for long-acting insulins. In February 2013, Novo Nordisk received a Complete Response Letter from the US Food and Drug Administration (FDA) in which the agency requested additional cardiovascular safety data from a dedicated cardiovascular outcomes trial before the review of the New Drug Application can be completed. While Novo Nordisk remains confident about the cardiovascular safety of Tresiba® based on both its own interpretation of the data derived from the clinical development programme and reviews by the European and Japanese regulatory authorities, the company also recognises the importance of reassuring the FDA about the cardiovascular safety. Hence, in October 2013, a dedicated clinical trial, named DEVOTE, was initiated to rule out any excess cardiovascular risk. DEVOTE is a double-blind trial, using insulin glargine as comparator, and is expected to include around 7,500 type 2 diabetes patients who have existing or high risk of cardiovascular disease. Novo Nordisk expects to have sufficient data to support a prespecified interim analysis within two to three years and to complete the study within four to six years from initiation. Thereby Novo Nordisk passed a significant milestone in the process of making Tresiba® available for people with diabetes in the US.

#### Tresiba® study results

Translating the results from clinical trial programmes into real advances in clinical practice can be challenging, especially since new medicines are often utilised in patients who are not responding well to available therapies. However, recent findings from Marc Evans, a clinician investigator in the UK, provide some important insights into how much value Tresiba® can bring to patients who are experiencing challenges with other insulins. Dr Evans studied 25 consecutive patients who were experiencing poor glucose control and frequent low blood sugar with either insulin glargine or Levemir® (insulin detemir). He found that when switched to Tresiba®, these patients improved their glucose control (in both type 1 and type 2 diabetes) and substantially reduced the frequency of low blood sugar episodes.<sup>2</sup>

[Back to Contents](#)

## 26 OUR BUSINESS

## Changing diabetes where it matters most

It has been almost a decade since Novo Nordisk launched Changing Diabetes®, its promise to people with diabetes to help them live a better life. Much has been achieved in this time, but a lot still needs to be done.

**N**ovo Nordisk's core responsibility to people with diabetes and to society is to deliver innovative, high-quality products. We have a very diverse insulin portfolio, from human insulins to modern insulin analogues," says Jakob Riis, executive vice president of Marketing & Medical Affairs. "Our core focus is to drive innovation and develop even better products to help people achieve the best possible outcome of their treatment."

As a world leader in diabetes care, Novo Nordisk not only produces insulin, but also works to ensure that it reaches the hands of those who need treatment and care worldwide. "We strive to make insulin accessible for more people living at the base of the economic pyramid, and we'll continue to offer human insulin at very low prices in developing countries," explains Jakob Riis.

While delivering products will always remain Novo Nordisk's number one priority, the efforts to change diabetes go beyond medicine. "Our goal is to make a difference to patients, and we know that we can only get part of the way with our products. This is why our Changing Diabetes® activities are important," points out Jakob Riis.

"Access to health is a human right, and Changing Diabetes® is Novo Nordisk's response to the global diabetes challenge. A key element is our strategy for global access to diabetes care, which we renewed in 2013. It is global in scope and part of our business model. Basically, we will stop diabetes ruining people's lives," explains Charlotte Ersbøll, corporate vice president of Corporate Stakeholder Engagement. "We would like to see a world where everyone with diabetes is diagnosed, everyone who is diagnosed gets treated and everyone treated can live their life to the full," she adds.

That is why Novo Nordisk is working around the world together with its partners to break the diabetes 'Rule of Halves'. [Read more on pp 22–23](#).

### The challenge is global, the solutions local

"The challenges of living with diabetes are different from country to country and person to person, so we partner with governments

and local stakeholders to identify the most pressing health needs and ways in which we can achieve the biggest impact," explains Charlotte Ersbøll. For countries where improving understanding of diabetes and its prevention is of the utmost importance, Novo Nordisk works to raise awareness, for example through activities on World Diabetes Day and by organising high-level national and international diabetes leadership forums with policymakers. More urgent in some countries is the need to increase diagnosis of diabetes and improve access to healthcare. In these areas Novo Nordisk is working with local partners to develop screening programmes, build capacity by training healthcare professionals, and establish clinics and networks to strengthen the existing healthcare infrastructure.

### Ambitious long-term target

"Ten years ago diabetes was not recognised as having a direct impact on development," says Charlotte Ersbøll. "The world knew diabetes was increasing in high-income countries such as the US, but didn't understand the implications of the rising prevalence of diabetes in developing countries. Today non-communicable diseases, including diabetes, are recognised as the biggest killer globally and therefore increasingly important on the global health agenda."

Novo Nordisk has set a long-term global target of providing quality diabetes care products to 40 million people by 2020. It builds on the belief that the way in which the company addresses a global health issue must be linked to its commercial offering; otherwise it is not sustainable in the long term. Today, Novo Nordisk provides diabetes care products to more than 24 million people.

"With our '40by20' long-term target we hope to make a significant contribution to the World Health Organization's target of decreasing mortality from non-communicable diseases such as diabetes by 25% by 2025," adds Charlotte Ersbøll.

[Back to Contents](#)

**Team Novo Nordisk has raced more than 9,500 km in 55 races since its launch in December 2012.**



**Inspire people with diabetes through Team Novo Nordisk**

"Ultimately, diabetes shouldn't restrict the lives of children or adults no matter where they live," says Jakob Riis. "This is why we support Team Novo Nordisk, the world's first all-diabetes pro-cycling team. The team's mission is to educate, empower and inspire those affected by diabetes. We want people to say 'I manage my diabetes, it doesn't manage me'." In total, Team Novo Nordisk consists of more than 80 cyclists, triathletes and runners who all have diabetes.

**Training apprentices in China.**



**Building healthcare capacity**

Healthcare professionals who are capable of detecting and treating diabetes are needed to catch up with the accelerating growth in the prevalence of diabetes. In China, Novo Nordisk, the government and local partners collaborate to increase quality diabetes care. As of October 2013, 2,076 apprentices have been trained and people across 830 counties have benefited from improved diagnosis and treatment. Another example is the new REACH programme in which Novo Nordisk-owned Steno Diabetes Center is scaling up its efforts by establishing an education centre in various countries in Asia. Once fully rolled out, the programme, which is funded by the Novo Nordisk Foundation, is expected to train more than 9,200 healthcare professionals globally each year.

**Patsy Left Hand Bull** is a tribal elder of the Lakota Sioux tribe in the Rosebud Reservation.



**Supporting vulnerable populations**

People living in vulnerable communities are often overlooked if they live in high-income countries, but they experience disproportionately high levels of diabetes compared with the rest of the population. Novo Nordisk recently helped the Rosebud Sioux tribe of South Dakota in the US improve diabetes care. The project includes a mobile health unit for travelling to remote areas of the reservation, a wellness centre and a programme to certify diabetes educators.

**The World Diabetes Foundation**

The World Diabetes Foundation was established by Novo Nordisk in 2002 as an independent trust with the vision of being a catalyst for change in developing countries. Since 2002, Novo Nordisk has donated around 1.1 billion Danish kroner to the Foundation. The largest share (37%) is spent on strengthening healthcare systems and building healthcare capacity. As of October 2013, 7,138 clinics had been established or strengthened, 4.6 million patients had been treated and 221,935 healthcare professionals trained.

**Eliodoro Gonzales** lives in Bolivia. He has type 1 diabetes and lost his legs due to diabetes complication.



**In most of Africa there is a lack of knowledge about diabetes.**



**Reaching the base of the pyramid**

People who earn 1,500–3,000 US dollars per year constitute more than 1 billion people. With some disposable income, but difficulties in accessing healthcare services, they belong to the base of the global economic pyramid. Novo Nordisk has launched projects in Kenya, India and Nigeria to bring diabetes care to these people. Through public-private partnerships, integrated solutions are pursued to supply insulin and diagnosis as well as quality treatment and care. One example is the establishment of 'One-Stop-Shops' in Nigeria, where people with diabetes are offered guidance on how to manage their diabetes, blood glucose testing and easy and fast access to insulin.

**Ranjith** is enrolled in the Changing Diabetes® in Children programme in India.



**Changing Diabetes® in Children**

In some developing countries, the life expectancy for children with type 1 diabetes is less than one year. In 2010, Novo Nordisk committed 75 million Danish kroner over five years to provide free insulin and care to children as part of its Changing Diabetes® in Children programme. The programme is a collaboration with local partners including ministries of health and the World Diabetes Foundation. Since 2010, 93 clinics have been established and over 4,150 local healthcare professionals have received the proper training and education to treat children. More than 11,700 children in nine countries across Africa and Southeast Asia have been enrolled in the programme.



[Back to Contents](#)

28 OUR BUSINESS

Is  
**obesity**  
a disease?

The increasing prevalence of obesity is no longer just an issue for high-income countries; the number of people who are overweight or obese is rising to record-breaking levels in low- and middle-income countries too. Without doubt, obesity is a growing threat to global health as it has many potentially life-threatening complications, not least type 2 diabetes. With liraglutide 3 mg, Novo Nordisk hopes to be able to offer a new treatment option for some people with obesity.

**A**ccording to the World Health Organization, being overweight or obese is the fifth leading risk for deaths worldwide, and is linked to more deaths globally than being underweight. In the US, where more than 35% of adults, or some 100 million people, are obese,<sup>1</sup> the American Medical Association recently recognised obesity as a disease. In 2011, a US congress committee urged the US Food and Drug Administration (FDA) to take steps to support the development of new treatments for obesity. The US isn't the only country sounding the alarm over the obesity epidemic. Worldwide there appears to be a new willingness to address obesity. The problem isn't necessarily obesity itself, it's that obesity can have many serious – even life-threatening – health consequences. Known co-morbidities including heart disease, hypertension, type 2 diabetes, sleep apnoea and some types of cancer<sup>2–5</sup> reduce life expectancy for people with obesity by 5–10 years. With increased BMI<sup>6,7</sup> (see box on p 29) the risk of these complications increases and, as a consequence, obesity has a huge cost implication for healthcare systems.<sup>8</sup> Yet, many people with obesity are unaware how it might affect their health. "Some people who are overweight or obese may never experience any health issues," explains Mads Krogsgaard Thomsen, executive vice president and chief science officer. "For these people, obesity may be less of a health concern. What we're concerned about are the people who have a BMI of 35 or more and a significantly elevated risk of complications such as diabetes, prediabetes or sleep apnoea, or indeed may already have these co-morbidities. It's our vision to offer a medical treatment to help these people specifically."

**Moderate weight loss has significant health benefits**

Lifestyle interventions, including a healthy diet and increased physical activity, should always be part of the treatment for people with obesity. It's recognised that a moderate weight loss of 5–10%

significant health benefits.<sup>9–15</sup> However, with most people not managing to achieve and maintain this level of weight loss with diet and exercise alone, other treatment options are necessary. "In the past, when medicines with an acceptable efficacy and safety profile were lacking and after diet and exercise had failed, doctors may have been reluctant to engage in dialogue with patients about obesity," says Heather Millage, corporate vice president and responsible for bringing liraglutide 3 mg to the market. "We hope obesity care will improve when more tools – in particular liraglutide 3 mg – are available for the treatment of this disease." Liraglutide 3 mg, Novo Nordisk's once-daily GLP-1 therapy, has recently completed the fourth phase 3a trial as part of SCALE™, the clinical development programme for obesity treatment.

"Liraglutide is a fascinating molecule," points out Mads Krogsgaard Thomsen. "Back in 1997, our research scientists suggested it could be efficacious for the treatment of type 2 diabetes, as well as obesity. We've therefore been investigating this molecule for the last 15 years. If approved, it'll be the first and only product to treat obesity based on physiological regulation of appetite."

**A natural hormone**

Liraglutide 3 mg is 97% similar to human GLP-1, a gut hormone that produces the sensation of fullness and decreases hunger signals when eating. Thereby it reduces appetite and food intake. In addition, liraglutide 3 mg stimulates the release of insulin in response to glucose to maintain the right levels of glucose in the blood. "GLP-1 is a natural hormone in the body, so with liraglutide 3 mg we're using one of the body's own mechanisms to tackle obesity," says Mads Krogsgaard Thomsen. "In clinical trials, four out of 10 patients who took

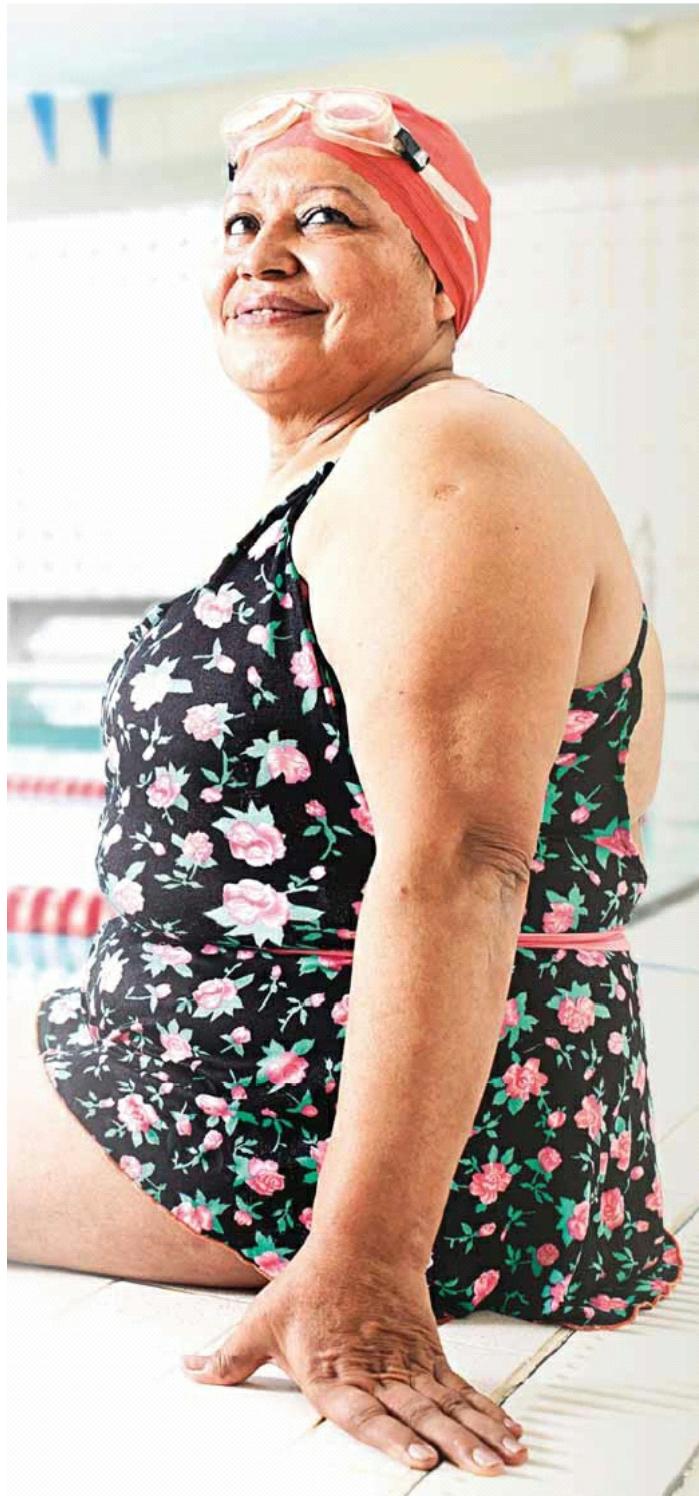
liraglutide 3 mg during one year lost 10% of their body weight. And the majority of patients who had prediabetes at the beginning of the trial and who took liraglutide 3 mg reverted to a normal glucose level." In fact, the majority of people with obesity treated with liraglutide 3 mg in the largest trial in the development programme achieved a clinically relevant weight loss of 5%. In one of the trials that extended for 104 weeks, weight loss achieved after one year was maintained for two years. Safety has been a key issue for obesity treatments, with several drugs being withdrawn due to safety concerns. However, a lot is already known about the safety profile of liraglutide. Under the brand name Victoza®, liraglutide has been on the market since 2009 in 1.2 mg and 1.8 mg doses for the treatment of type 2 diabetes.

**Stigmatisation of people with obesity**

While liraglutide 3 mg looks promising for the treatment of obesity, and with early research ongoing into other approaches to treating obesity, there are still challenges ahead. One is that many doctors, based on past experience, are reluctant to prescribe antiobesity medications due to concerns that the benefits don't outweigh the risks of treatment. Another is that obesity medications aren't widely reimbursed. The latter is to a large extent the result of a false assumption that all people with obesity can effectively lose weight just by changing their lifestyle – exercise more and eat less. For most this has proven exceedingly difficult, if not impossible, despite many attempts. It is this group – often stigmatised due to their weight and suffering from the complications of obesity – that may benefit from treatment with an obesity medication in combination with lifestyle changes and diet.

"There are many myths and a lot of stigmas when it comes to the science of obesity and its treatment. We need to remove the stigma and raise awareness that safe and effective treatment options can improve lives. This is what Novo Nordisk has been doing successfully with type 2 diabetes and we think we can do it with obesity too," says Heather Millage.

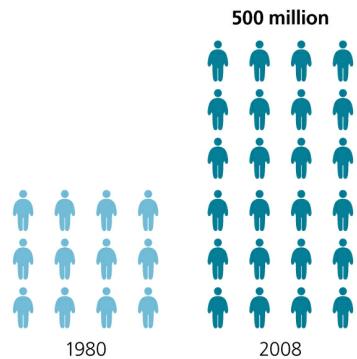
[Back to Contents](#)



Maria Lopez is one of the 100 million obese people in the US. Her BMI is 33.

29

### The number of adults with obesity has doubled since 1980



Worldwide rates of obesity have doubled since 1980, with more than 500 million adults classified as obese in 2008 – more than 10% of the world's adult population (World Health Organization's global estimates from 2008).

#### Definition of obesity

Obesity is defined as abnormal or excessive fat accumulation that may impair health for people with a BMI over 30. BMI provides the most convenient population-level measure of overweight and obesity currently available.<sup>16</sup> BMI itself, however, does not define health risk.

#### The role of hormones in obesity

The understanding of the biological factors contributing to weight gain and obesity is rapidly evolving. There is increased focus on the role of hormones and new research clearly indicates that much more is involved in the progression from normal body weight to obesity than just a person's lifestyle and eating habits.<sup>17</sup> The regulation of appetite and food intake is a complex process involving multiple hormones that transmit signals between the organs that receive the food (the intestines or gut) and the brain. After a meal, the gut responds to food by producing several hormones that tell the brain to increase the feeling of fullness while reducing feelings of hunger. One of these hormones is GLP-1, which has been found to play an important role in regulating appetite.<sup>18</sup> As a GLP-1 analogue, liraglutide directly addresses some of the underlying biological mechanisms of obesity. Novo Nordisk is committed to research into and further exploration of the role of hormones in obesity and weight management, and the development of liraglutide is a first step in this process.

[Back to Contents](#)

30 OUR BUSINESS

# An important factor of life

For people living with haemophilia A or B, there hasn't always been a great deal of choice when it comes to treatment. With NovoSeven®, Novo Nordisk helps about 5% of these people – but with the launch of NovoEight®, the company will be able to help many more.

Novo Nordisk addressed a huge unmet medical need in 1996 when it launched the first ever recombinant treatment for people with haemophilia with inhibitors. Today NovoSeven® is still an important treatment option for the small part of the haemophilia community who have inhibitors. Now, Novo Nordisk is offering another product for people in the haemophilia community by launching a recombinant factor VIII product (turoctocog alfa) for people with haemophilia A. "While there are already similar products available for this group of people, NovoEight® should not be underestimated," says Stephanie Seremetis, chief medical officer, Haemophilia.

"We've tried to improve on what is available and I think we've achieved this. NovoEight® is technically a different product from our competitors'. We've established a production process focusing on providing a new, highly purified and well-defined molecule and I believe this is important for both safety and efficacy. Of all licensed factor VIII products, NovoEight® has undergone the largest pre-approval programme ever carried out, which also includes a paediatric study. We therefore have a lot of data to document the safety and efficacy of our product."

## Building on confidence

In the phase 3 trial, NovoEight® demonstrated good efficacy in preventing and treating bleeds and had no confirmed inhibitor development. NovoEight® has now been approved in the US, the EU and Japan for the treatment and prophylaxis of bleeding in patients with haemophilia A. In January 2014 Germany was the first country to launch NovoEight®, and Novo Nordisk expects to launch the product in more European countries and in Japan during the year. Launch in the US is expected after April 2015, awaiting the expiration of existing patents.

"NovoEight® is very important for us as a company as we want to be a true partner for people with haemophilia and take a leadership role in this market – and we can't do that without a treatment option for people with haemophilia A," explains Paul Huggins, corporate vice president and responsible for bringing NovoEight® to the market. "Patients and doctors have grown to know and have confidence in NovoSeven®. We want to build on that confidence by providing another option for physicians that's based on advanced purification technology."

## A paradigm shift in treatment

Novo Nordisk is also developing a long-acting recombinant factor VIII (N8-GP) and factor IX (N9-GP). The latter holds the promise of changing treatment



Image of the turoctocog alfa molecule based on X-ray crystallography data. Turoctocog alfa is the active compound in NovoEight®.

options for people with haemophilia B. "Our strong clinical trial results have shown that prophylactic treatment with N9-GP reduces the number of bleeding episodes per year to a very large extent," says Stephanie Seremetis.

Unfortunately, the expansion of manufacturing capacity for N9-GP didn't progress as fast as planned, and Novo Nordisk therefore had to shorten the duration of one of the clinical trials. This, understandably, caused much frustration among both patients in the trial and their doctors. In addition to developing products for the wider haemophilia community, Novo Nordisk remains committed to smaller patient groups – as illustrated by the development and approval in major markets of NovoThirteen® for the treatment of a rare bleeding disorder caused by congenital factor XIII deficiency, which around 1,000 people suffer from worldwide.

## Haemophilia

Haemophilia is an inherited or acquired bleeding disorder that prevents blood from clotting. People with haemophilia lack, either partially or completely, an essential clotting factor needed to form stable blood clots. Internal bleeding into the joints, muscles and other tissues can cause severe pain, joint damage and disability. The treatment for haemophilia involves intravenous administration of replacement clotting factors. Treatment may be administered when bleeding occurs or, increasingly, on a preventive basis (prophylactic treatment).

People with haemophilia A may have either a decreased ability or total inability to produce clotting factor VIII. Approximately 350,000 people have haemophilia A globally. However, the disease is severely under-diagnosed in developing countries.

People with haemophilia B have deficiencies in producing clotting factor IX. Haemophilia B is inherited in the same way as haemophilia A, but is five times less common (70,000 people worldwide).

Around 3,500–4,500 people with haemophilia worldwide have high-titre inhibitors.

## Living with haemophilia

HERO (Haemophilia Experiences, Results and Opportunities) is an international study that aims to build an understanding of life with haemophilia, seen from the perspective of people with haemophilia, their families and their healthcare providers. Read more about the study, which is supported by Novo Nordisk's programme Changing Possibilities in Haemophilia®, at novonordisk.com/hero.

[Back to Contents](#)

## Novo Nordisk's **FIVE REGIONS**



Novo Nordisk markets its products in more than 180 countries. Despite the differences in terms of economic development, political systems and healthcare infrastructure between these countries, Novo Nordisk's business model is fundamentally the same all over the world.

**N**ovo Nordisk has employees in 75 countries. They share the common ambition to be the country's leading pharmaceutical company within the selected disease areas, both in commercial terms and when it comes to making a positive change for patients. Key to achieving this ambition are biological pharmaceuticals with new, distinct properties that Novo Nordisk's researchers have invented and developed. These products, for example NovoRapid®/ NovoLog®, Levemir® and Victoza®, are what make up the bulk of Novo Nordisk's revenues in all of its five business regions. In addition, Novo Nordisk offers – and is committed to continue offering – lower-priced products in the form of traditional human insulin in countries where there's still a significant demand for such products.

### Creating value for customers

Novo Nordisk markets its products the same way globally by sharing clinical knowledge about the products with doctors, so that they can make an informed choice about whether these products are right for their patients. At the same time, payers and administrators – typically public health systems and private health plans – are presented with evidence about the cost efficiency of the products, in order to make informed decisions about pricing and reimbursement. Moreover, Novo Nordisk organises and supports education of healthcare professionals in managing diabetes, and engages in activities aimed at improving awareness, prevention and diagnosis of the disease.

### Organisation

Novo Nordisk is a firm believer in having wholly owned affiliates and expanding them organically as the market develops. While

other pharmaceutical companies may build a presence through the acquisition of local companies, joint ventures or rented sales forces, Novo Nordisk prefers to hire its own people and train them to become the best. This is also seen as the best way to convey and preserve a strong company culture.

### Competitors

In its all-important insulin market, Novo Nordisk's main competitors are the same all over the world: Eli Lilly and Sanofi. In addition, there are local competitors in some countries such as China and India. However, they are not innovation-based and primarily offer human insulin. So far, these companies haven't been able to gain significant market shares. In the biopharmaceuticals business, Novo Nordisk faces competition from a broader number of pharmaceutical companies, in some markets including producers of biosimilar medicines (products that are similar but not identical to an original medicine). So far, biosimilar competition hasn't had a dramatic impact on the business, which has continued to grow at a global level.

### Regional differences

What almost all countries have in common is that the incidence of diabetes is increasing and that they're battling with how to tackle the situation most effectively. The countries differ, however, when it comes to the level of spending on diabetes care and in their ability and willingness to fund further investments in improving care, including the use of the latest advances in medical treatment. The following pages provide a review of Novo Nordisk's business in the five regions.

**CONTINUED ►**

[Back to Contents](#)

32

## ■ North America

The North American region consists of the US and Canada and is Novo Nordisk's largest in terms of sales, which isn't surprising given that the US is the world's largest pharmaceutical market. In 2012, total pharmaceutical sales in the US amounted to 327 billion US dollars, of which 6% was spent on products for treating diabetes. Novo Nordisk has experienced tremendous growth in the US in recent years. Since 2008, sales have more than doubled from 14 billion Danish kroner (3 billion dollars) to 37 billion kroner (7 billion dollars) in 2013. In the same period Novo Nordisk's organisation in the US, including research and development and production, has grown from around 3,700 employees to more than 6,100. The main drivers of sales have been – and continue to be – the portfolio of modern insulins and Victoza®. In 2013, sales of diabetes care products increased by 18% in local currencies in North America. This reflects continued market penetration by the modern insulins, especially

Levermir®, modest growth of human insulin and a 31% growth in sales of Victoza®, measured in local currencies. Sales of biopharmaceuticals – NovoSeven® and Norditropin® being the main products – grew by 16% in 2013, measured in local currencies. Norditropin® in particular did very well in 2013, which is due to both the very positive reception of the FlexPro® injection device and the very comprehensive support programmes that Novo Nordisk offers both healthcare professionals and patients.

### A complex healthcare system

The US healthcare system is complex as it involves multiple payers and intermediaries with complex interactions. Roughly half of all Americans are insured by their employers and one-third by the government through programmes such as Medicare and Medicaid, while around 15% are uninsured. The government figure is expected to increase significantly while the number of uninsured is expected to drop significantly in the coming years as a result of the Affordable Care Act, which is currently being implemented. To manage the purchase and delivery of healthcare, employers and the government contract with intermediaries such as health plans and pharmacy benefit managers (PBMs). These are often referred to as 'payers', but are in most cases managers of healthcare costs on behalf of payers. Health plans contract with

providers such as physician, hospital and pharmacy networks to provide the required service. They provide different levels of coverage based on the payers' willingness to pay for selected services for their employees. A PBM is an intermediary that contracts with payers and health plans to manage the pharmacy benefit for a specific population. Typical services include claims processing, managing enrollee eligibility, contracting pharmacy networks and managing rebate contracts with pharmaceutical companies.

The health plans use various methods for managing the use and cost of pharmaceuticals. Among the most widely used interventions are generic substitution, quantity limits, prior authorisation (which means that a medication will only be covered under certain conditions and subject to individual approval by the health plan) and tightly controlled Preferred Drug Lists.

### Growing pressures

Competitive pressures are growing in the managed healthcare industry, driving both consolidation through mergers and acquisitions and increasingly tough rebate negotiations with pharmaceutical companies. Novo Nordisk experienced the effects of the latter in the second half of 2013 when it lost coverage for NovoLog® and Victoza® for 2014 with Express Scripts National Preferred Formulary covering 45 million people in the US. Despite such pressures and increasing competition from other pharmaceutical companies, Novo





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[Back to Contents](#)

Nordisk maintains a competitive presence on the US market. The company's key diabetes care products have broad market access and are capturing market shares. In fact, in 2013 Novo Nordisk's three modern insulins were the only products with a growing volume market share in the US in the modern insulin category.

**Growing market for diabetes products**

Novo Nordisk holds around 29% of the total US market for diabetes care medications and 37% of the insulin market, measured in value. The insulin market is expected to continue growing in volume in the coming years due to the increasing number of people with diabetes, many of whom will require insulin treatment. Moreover, in the US, only around 41% of insulin volume is delivered in a pen system such as Novo Nordisk's FlexPen®, while it is more than 95% in Europe. This means there is still significant potential to upgrade treatment in the US. In 2014, Novo Nordisk expects to introduce its newest pen system, FlexTouch®, with certain insulin products.

Novo Nordisk is the market leader within GLP-1-based therapies in the US, where Victoza® has a value market share of around 67%. The market itself experienced decelerating growth in 2013 due to questions being raised about potential pancreatic side effects. [Read more on pp 38–41](#). Victoza®, however, continues to expand its share of the GLP-1 market and has further consolidated this position with the support of a new nationwide TV campaign.

It's Novo Nordisk's ambition to sustain the strong performance, despite the dynamic business environment, by consolidating the diabetes market leadership position through the modern insulins and Victoza®.

To further strengthen the presence in the US, Novo Nordisk's US affiliate has expanded its field force several times in recent years. The latest expansion was announced in 2013 with the addition of more than 350 new representatives, who after an intensive period of training will be in the field by April 2014.

**Preparing for a new market**

The US affiliate is preparing to enter a new market for the medical treatment of obesity with liraglutide 3 mg, which was filed for regulatory review with the US Food and Drug Administration (FDA) in December 2013. [Read more about obesity on pp 28–29](#).

**Developments to look out for**

In February 2013, the FDA requested more data on the cardiovascular safety profile of Tresiba® (insulin degludec) before it could complete its review of Novo Nordisk's application. In response, Novo Nordisk initiated a cardiovascular outcomes trial involving 7,500 patients. [Read more on pp 24–25](#).

Another event that may have an impact on the insulin market is Sanofi's basal insulin product, insulin glargine, which will lose US patent protection in 2015. Eli Lilly has submitted a biosimilar version of insulin glargine for regulatory approval, and Sanofi itself is developing a stronger formulation of insulin glargine. How, and to what extent, such events will change the market dynamics is not possible to predict at this point in time. In the GLP-1 area, several new products are likely to enter the market in the coming years.

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Sales in North America .....

Year	Sales (DKK billion)
2009	~18
2010	~22
2011	~26
2012	~33
2013	~40 (+14%)



